system. Smoking-induced reduction in skin blood flow also can be antagonized by a vascular vasopressin antagonist, which suggests a role for vasopressin in mediating some cardiovascular responses *(2)*.

The cardiovascular effects of oral snuff have been examined systematically in only one study *(13)*. Changes in heart rate and blood pressure that are similar in magnitude to those of cigarette smoking were observed. However, the time course appears to be slower than the response to cigarette smoking, with maximum effects observed at 5 to 10 minutes after a dose of oral tobacco. Similar findings, along with increased myocardial contractility and coronary, femoral, and renal blood flow, were also noted in anesthetized dogs after the administration of oral tobacco *(13)*. Thus it appears that single doses of smokeless tobacco can produce hemodynamic effects that are similar to those of cigarette smoking. Whether such changes are sustained throughout the day with repeated daily doses remains to be established.

Central Nervous System

Although smokers give different explanations for why they smoke, most agree that smoking produces arousal, particularly with the first few cigarettes of the day, as well as relaxation, especially in stressful situations *(14)*. Desynchronization, decreased alpha and theta activity, and increased alpha frequency that is consistent with arousal are the usual electroencephalographic responses to cigarette smoking *(15,16)*. These effects are blocked by mecamylamine, a centrally active nicotinic receptor antagonist, which indicates a role for nicotinic cholinergic receptor activation *(17)*. Tobacco abstinence is associated with effects that are opposite those of smoking, namely, increased alpha power and reduced alpha frequency *(15,18)*.

Endocrine System

Cigarette smoking and nicotine have been reported to increase circulating levels of catecholamines, vasopressin, growth hormone, cortisol, ACTH, and endorphins *(3,19,20)*.

Nicotine inhibits the synthesis of prostacyclin in rabbit aorta and human peripheral veins and the hypoxia-induced release of prostacyclin from rabbit hearts *(21)*. Cigarette smoking has been reported to decrease the urinary excretion of prostacyclin metabolites in humans, which supports the prediction from animal studies *(22)*. Prostacyclin has antiaggregatory and vasodilating actions that are believed to play a homeostatic role in preventing vascular thrombosis.

Nicotine, Smokeless Tobacco, and Human Diseases

As attested to in the Surgeon General's reports since 1964, smoking is a major risk factor for coronary and peripheral vascular disease, cancer, chronic obstructive lung disease, peptic ulcer disease, and repro-

ductive disturbances, including prematurity. Tobacco smoke is a complex mixture of chemicals, including carbon monoxide, many of which are believed to contribute to human disease. Smokeless tobacco likewise exposes users to a number of chemicals, particularly nicotine. Nicotine may play a contributory or supportive role in the pathogenesis of many smoking-related diseases. That nicotine causes human disease de novo has not been proven; however, its potential health consequences deserve serious consideration. More direct data on its causal role are needed.

Coronary and Peripheral Vascular Disease

Nicotine may contribute to atherosclerotic disease by actions on lipid metabolism, coagulation, and hemodynamic effects. Compared to nonsmokers, cigarette smokers have elevated levels of low density (LDL) and very low density lipoproteins (VLDL) and reduced levels of high density lipoproteins (HDL). This profile is associated with an increased risk of atherosclerosis *(23)*. It is hypothesized that nicotine, by releasing free fatty acids, increases the synthesis of triglycerides and VLDL by the liver, which in turn results in decreased HDL production.

In most studies, the blood of smokers is shown to coagulate more easily *(24)*, platelets are found to be more reactive, and platelet survival is shortened when compared to nonsmokers *(25)*. Thrombosis is believed to play a role that promotes the growth of vascular endothelial cells that contribute to the atherosclerotic plaque. The importance of nicotine as a determinant of platelet hyperreactivity is supported by a study that shows an apparent relationship between nicotine concentrations after smoking different brands of cigarettes and platelet aggregation response *(26)*. Nicotine may affect platelets by releasing epinephrine, which is known to enhance platelet reactivity; by inhibiting prostacyclin, an antiaggregatory hormone that is secreted by endothelial cells; or perhaps directly. Finally, by increasing the heart rate and cardiac output, nicotine increases blood turbulence and may promote endothelial injury. Although several potential mechanisms for promoting atherogenesis have been considered, nicotine has not yet been demonstrated to accelerate atherosclerosis in experimental animals.

Nicotine may play a role in causing acute coronary events. Myocardial infarction can occur with one or more of three precipitants: thrombosis, excessive oxygen and substrate demand, and coronary spasm. Nicotine can promote thrombosis as discussed previously. Nicotine increases the heart rate and blood pressure and, therefore, myocardial oxygen consumption. Coronary blood flow increases in a healthy person to meet the increased demand. In the presence of coronary heart disease, ischemia may develop and myocardial dysfunction may occur. Nicotine may induce coronary spasm by sympathomimetic actions or by the inhibition of prostacyclin. Coronary spasm has recently been reported to occur during cigarette smoking *(27)*. All of the above may contribute

to the precipitation of acute myocardial infarction in a person with preexisting coronary atherosclerosis.

Cigarette smoke exposure decreases the ventricular fibrillation threshold after experimental myocardial infarction in dogs *(28)*. How much of this effect is due to nicotine and how much is due to carbon monoxide have not been established. Sudden cardiac death in smokers might result from ischemia, as discussed above, combined with the arrhythmogenic effect of increased circulating catecholamines.

Hypertension

Cigarette smoking has not been associated with an increased prevalence of hypertension. However, a recent preliminary report suggested higher blood pressure in young men who used smokeless tobacco compared to cigarette smokers or nonsmokers *(29)*. Smokers who have essential hypertension experience an accelerated progression of vascular and renal disease. Nicotine may contribute to such a process by producing vasoconstriction or enhancing coagulation. There also may be other interactions with hypertensive disease. For example, a patient with a pheochromocytoma developed paroxysmal hypertension and angina pectoris following the use of oral snuff *(30)*. In a controlled situation, blood pressure was recorded to increase from 110/70 to 300/103 with a heart rate increase from 70 to 110 within 10 minutes after the use of oral snuff. Rechallenge after surgery for the pheochromocytoma revealed only the usual blood pressure increase.

Peptic Ulcer Disease

Smoking is strongly related to the prevalence of peptic ulcer disease, and failure to stop smoking is the major predictor of failure to respond to ulcer therapy *(31)*. Smoking decreases pancreatic fluid and bicarbonate secretion that result in greater and more prolonged acidity of gastric fluid of the duodenal bulb *(32)*. Similar effects after the infusion of nicotine have been reported in animals *(33)*. The swallowing of tobacco juice that contains large concentrations of nicotine may conceivably have local effects and therefore elicit added concern for the use of smokeless tobacco.

Pregnancy

Smoking is a major risk factor for low birth weight and, consequently, fetal morbidity and mortality *(34)*. Tobacco smoke may influence the fetus either through alterations in maternal physiology that limit the nutrient flow to the fetus or by the transplacental passage of smoke components that have direct effects on the fetus. The factors that are considered most likely to affect the fetus are carbon monoxide and nicotine. Carbon monoxide inhalation has been shown to increase carboxyhemoglobin in both maternal and fetal blood that possibly limits oxygen supply to the fetus *(35)*. However, while newborn infants

of smoking mothers have higher concentrations of carboxyhemoglobin than do neonates of nonsmokers, there are only trivial differences in hemoglobin concentrations, hematocrit, and various characteristics of hemoglobin *(36)*. Thus it is difficult to explain an adverse effect that is based on chronic hypoxia due to carbon monoxide in tobacco smoke. It is more likely that nicotine is important in causing adverse effects.

The effects of nicotine on the fetus may include a reduction of uterine blood flow or a direct effect on fetal function *(37,38)*. The presence of nicotine and its principal metabolites has been demonstrated in the umbilical cord blood and urine of newborn infants of smoking mothers, as well as in amniotic fluid, indicating transplacental passage *(39)*.

Nonnicotine-Related Adverse Metabolic Consequences

Certain brands of chewing tobacco and snuff contain glycyrrhizinic acid, which is also an ingredient of licorice. Glycyrrhizinic acid has potent mineralocorticoid hormone activity that can result in potassium wasting. Two patients who were heavy users of oral smokeless tobacco developed severe hypokalemia with muscle weakness (and in one case, evidence of muscle breakdown) that apparently was due to the ingestion of large amounts of this substance *(40)*. Smokeless tobacco also contains large amounts of sodium *(41)* that, if swallowed, may aggravate hypertension or cardiac failure.

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CONCLUSIONS

1. The use of smokeless tobacco products can lead to nicotine dependence or addiction.
2. An examination of the pharmacokinetics of nicotine (i.e., nicotine absorption, distribution, and elimination) resulting from smoking and smokeless tobacco use indicates that the magnitude of nicotine exposure is similar for both.
3. Despite the complexities of tobacco smoke self-administration, systematic analysis has confirmed that the resulting addiction is similar to that produced and maintained by other addictive drugs in both humans and animals. Animals can learn to discriminate nicotine from other substances because of its effects on the central nervous system. These effects are related to the dose and rate of administration, as is also the case with other drugs of abuse.
4. It has been shown that nicotine functions as a reinforcer under a variety of conditions. It has been confirmed that nicotine can function in all of the capacities that characterize a drug with a liability to widespread abuse. Additionally, as is the case with most other drugs of abuse, nicotine produces effects in the user that are considered desirable to the user. These effects are caused by the nicotine and not simply by the vehicle of delivery (tobacco or tobacco smoke).
5. Nicotine is similar on all critical measures to prototypic drugs of abuse such as morphine and cocaine. The methods and criteria used to establish these similarities are identical to those used for other drugs suspected of having the potential to produce abuse and physiologic dependence. Specifically, nicotine is psycho-

active, producing transient dose-related changes in mood and feeling. It is a euphoriant that produces dose-related increases in scores on standard measures of euphoria. It is a reinforcer (or reward) in both human and animal intravenous self-administration paradigms, functioning as do other drugs of abuse. Additionally, nicotine through smoking produces the same effects, and it causes neuroadaptation leading to tolerance and physiologic dependence. Taken together, these results confirm the hypothesis that the role of nicotine in the compulsive use of tobacco is the same as the role of morphine in the compulsive use of opium derivatives or of cocaine in the compulsive use of coca derivatives.

6. The evidence that smokeless tobacco is addicting includes the pharmacologic role of nicotine dose in regulating tobacco intake; the commonalities between nicotine and other prototypic dependence-producing substances; the abuse liability and dependence potential of nicotine; and the direct, albeit limited at present, evidence that orally delivered nicotine retains the characteristics of an addictive drug.

7. Several other characteristics of tobacco products in general, including smokeless tobacco, may function to enhance further the number of persons who are afflicted by nicotine dependence: nicotine-delivering products are widely available and relatively inexpensive; and the self-administration of such products is legal, relatively well tolerated by society, and produces minimal disruption to cognitive and behavioral performance. Nicotine produces a variety of individual-specific therapeutic actions such as mood and performance enhancement; and the brief effects of nicotine ensure that conditioning occurs, because the behavior is associated with numerous concomitant environmental stimuli.

8. All commonly marketed and consumed smokeless tobacco products contain substantial quantities of nicotine; the nicotine is delivered to the central nervous system in addicting quantities when used in the fashion that each form is commonly used (or as recommended in smokeless tobacco marketing campaigns).

9. Since the exposure to nicotine from smokeless tobacco is similar in magnitude to nicotine exposure from cigarette smoking, the health consequences of smoking that are caused by nicotine also would be expected to be hazards of smokeless tobacco use. Areas of particular concern in which nicotine may play a contributory or supportive role in the pathogenesis of disease include coronary artery and peripheral vascular disease, hypertension, peptic ulcer disease, and fetal mortality and morbidity.

RESEARCH NEEDS

Available data clearly support the view that nicotine produces behavioral and physiologic dependence and has effects on all critical dimensions exemplified by a drug with a profile of high abuse liability. Nevertheless, the resolution of several questions is essential. These questions revolve around the relationships between the several forms of tobacco use. They parallel and have commonalities with important issues in other forms of drug abuse (e.g., cocaine). There are several major research areas that could provide data of potential public health significance.

The first area of research is the relationship between the rate of nicotine administration and abuse liability. Existing data suggest that the slowest commercially available nicotine-releasing preparation, nicotine gum, has a lower abuse liability than the fastest commercially available nicotine-releasing preparation, cigarettes. These facts further suggest the possibility that there might be quantifiable differences in abuse liability among tobacco product forms.

The second area of research importance involves the relationship between the initiation of one form of tobacco use, e.g., smokeless tobacco, and the use of other forms of tobacco, e.g., cigarettes. The relationships between common forms of tobacco use, the extent to which they are interchangeable, and the possibility that the use of one form of tobacco leads to the use of another need examination.

A third area of specific importance relates to the extent to which tobacco use, with its implicit acceptance, encourages other drug use. A related question is the extent to which exposure to drug effects, both neurologic and behavioral, modifies subsequent drug responses or establishes the conditions for other equally harmful drugs to become reinforcers. These issues follow from the observations that cigarette use is a major correlate (possibly a "stepping stone") of other kinds of drug dependence and that regular tobacco use generally leads to other forms of drug addiction.

A fourth area of research is prevention and treatment. Recent surveys indicate that youth attribute negligible risk to smokeless tobacco products, suggesting the possible need for education-based prevention approaches. Regarding treatment, it is plausible that nicotine gum treatment could be of even greater relative utility for smokeless tobacco users than for cigarette smokers because of the more similar pharmacokinetic profiles of smokeless tobacco- and gum-delivered nicotine compared to cigarette smoke-delivered nicotine.

The absorption and distribution characteristics of nicotine with the use of smokeless tobacco may differ from those of cigarette smoking. The pharmacodynamic and pharmacologic consequences of such differences may be important but require additional future research. Further studies to define more precisely the role of nicotine and of smokeless tobacco in the causation of diseases other than those that

involve the oral cavity are clearly needed. Specifically, research is needed to:

- Determine nicotine blood levels and time course in various populations of smokeless tobacco users, including established users.
- Determine the cardiovascular, hormonal, and metabolic effects of smokeless tobacco when used in a regular fashion throughout the day.
- Determine the influence of the rate of absorption of nicotine on the effects from smoking cigarettes and the use of smokeless tobacco.
- Using experimental studies, determine the effects of smokeless tobacco in users of different ages and high-risk status (i.e., patients with hypertension, coronary heart disease, peripheral vascular disease, and peptic ulcer).
- Using epidemiologic studies, determine the risk potential of the regular use of smokeless tobacco on the development of diseases such as coronary heart disease, peptic ulcer, and complications of pregnancy.